REMARKS

Claims 1-5, 9-18, and 22-28 are in this application. Claims 1 and 11 have been amended and claims 6, 7, 8, 19, 20, 21, 29 and 30 have been cancelled. Claims 24, 25 and 27 have been withdrawn.

Applicant again wants to thank the Examiner for the courtesy of conducting an interview with applicant's representative on February 24, 2010. The primary focus during the interview was a discussion of the Zamore reference and possible amendments to the claims.

According to the Examiner claims 1-23 and 26 are rejected under 35 USC 102(e) as being anticipated by Zamore et al. as evidenced by Aravin and Elbashir. This is respectfully traversed.

The present invention is clearly different from Zamore et al. in that the position(s) of a mismatch(es) is limited to one or more consecutive residues at the ends of the double-stranded part and/or only one residue at around the center of the double-stranded part. Claims 1 and 11 have been amended to exclude mismatches at any other positions.

The application relates to an improved siRNA to control its effect on suppressing the gene expression (paragraphs 0008 and 0009). A conventional siRNA i.e. an siRNA before improvement is described to have a sense and an antisense strands which are complementary to each other (paragraph 0019). The siRNA of the present invention is described to be improved based on the conventional siRNA in that a mismatch(es) is introduced into one or more consecutive residues at the ends of the double-stranded part and/or only one residue at around the center of the double-stranded part (paragraphs 0022 through 0030) and this provides support for the amendments to claims 1 and 11.

In addition, claims 4 and 17 recite that one additional mismatch is located at position 11-13 from the 3' end of the sense strand of the double-stranded part. miR-13b-2 has a mismatch at a different position.

Therefore, as the claims in this application are not anticipated by Zamore it is respectfully requested that the rejection be withdrawn.

The Examiner also states that claims 1-23 and 26 are rejected under 35 USC 103(a) as being unpatentable over Jayasena et al. , Khvorova et al., Elbashir et al and Holen et al.

This rejection is respectfully traversed.

The Examiner has maintained the rejection as a whole. According to the Examiner Jayasena et al. and Khvorova et al. disclose that the strands of the siRNA are more efficiently loaded into RISC when the ends are more weakly associated. In addition, it appears that the Examiner believes that it was well known in the art that mismatched base pairs decrease the stability of a duplex. Therefore, the Examiner maintains that those skilled in the art would have wanted to incorporate mismatches at the ends of the siRNA.

However, it is well known in the art that a single stranded RNA is more susceptible to degradation by RNase than a double stranded RNA. If the siRNA contains a single stranded structure at its end due to the presence of mismatches, the siRNA would be expected to be easily degraded by RNase in a cell, resulting in very low efficiency of RNAi. Therefore, those skilled in the art would never try to incorporate a mismatch(es) into siRNA molecules.

In fact, those skilled in the art have recognized it very important to prevent degradation of siRNA in a cell for designing an efficient siRNA. For example, Elbashir et al. discloses "(t)he siRNA user guide" on page 6885, the left column, and describes that the RNase resistance is preferred property of siRNA in the first paragraph ofthe guide. Elbashir et al. describe in the same paragraph that efficiently silencing siRNA duplexes must be selected to form a 19 bp double helix with 2 nt 3'-overhanging ends. It should be noted that the term "double helix" means a region composed of completely matched base pairs usually. Therefore, those skilled in the art would not conceive to incorporate a mismatch(es) into siRNA molecules.

Elbashir et at and Holen et al. do not disclose a mismatch(es) between the sense strand and the antisense strand of siRNA. The mismatches disclosed in Elbashir et al. and Holen et al. are between the antisense strand of siRNA and the target mRNA.

Elbashir et al. refers to mismatches on page 6884, the paragraph bridging left and rightcolumns. In this paragraph, sequence changes are introduced into the paired segments

of siRNA in order to examine the sequence specificity of target recognition. In the same paragraph, they describe that the sequence changes in one siRNA strand were compensated for in the complementary siRNA strand to avoid disturbing the base-paired siRNA duplex structure. Therefore, the mismatches disclosed in this paragraph are between the antisense strand of siRNA and the target mRNA.

Elbashir et al. also refers to mismatches on page 6885, the paragraph bridging left and right columns. This paragraph relates to the target recognition, i.e., the recognition of target mRNA by siRNA. In particular, this paragraph describes that siRNA duplexes may be able to discriminate mutant or polymorphic alleles in gene targeting experiments. In order to discriminate mutant or polymorphic alleles, siRNA should have a mismatch(es) relative to the target mRNA, not between the sense strand and the antisense strand of the siRNA. Therefore, the mismatches disclosed in this paragraph are between the antisense strand of siRNA and the target mRNA.

Holen et al. discloses dsRNA containing either one or two mismatches relative to an mRNA, as suggested by the Examiner. It is clear that the mismatches disclosed in Holen et al. are between the antisense strand of siRNA and the target mRNA. Accordingly, Elbashir et al. and Holen et al. do not provide any teaching for a mismatch(es) between the sense strand and the antisense .strand of siRNA, which is introduced into the claimed dsRNA.

Therefore, the rejection should be withdrawn.

It is submitted that the application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,

JANET 1. CORD
LADAS & PARRY LLP
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG. NO.33778 (212)708-1935